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SCIENTIFIC ARTICLE

Single photon emission computed tomography/spiral computed tomography fusion imaging for the diagnosis of bone metastasis in patients with known cancer

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Abstract
Purpose To evaluate single photon emission computed tomography (SPECT)/spiral computed tomography (CT) fusion imaging for the diagnosis of bone metastasis in patients with known cancer and to compare the diagnostic efficacy of SPECT/CT fusion imaging with that of SPECT alone and with SPECT + CT.
Materials and methods One hundred forty-one bone lesions of 125 cancer patients (with nonspecific bone findings on bone scintigraphy) were investigated in the study. SPECT, CT, and SPECT/CT fusion images were acquired simultaneously. All images were interpreted independently by two experienced nuclear medicine physicians. In cases of discrepancy, consensus was obtained by a joint reading. The final diagnosis was based on biopsy proof and radiologic follow-up over at least 1 year.
Results The final diagnosis revealed 63 malignant bone lesions and 78 benign lesions. The diagnostic sensitivity of SPECT, SPECT + CT, and SPECT/CT fusion imaging for malignant lesions was 82.5%, 93.7%, and 98.4%, respectively. Specificity was 66.7%, 80.8%, and 93.6%, respectively. Accuracy was 73.8%, 86.5%, and 95.7%, respectively. The specificity and accuracy of SPECT/CT fusion imaging for the diagnosis malignant bone lesions were significantly higher than those of SPECT alone and of SPECT + CT ($P<0.05$). Among 37 equivocal lesions revealed with SPECT, the diagnostic accuracy of bone lesions was 45.9% for SPECT + CT and 81.1% for SPECT/CT fusion imaging ($\chi^2=9.855$, $P=0.002$). The numbers of equivocal lesions were 37, 18, and 5 for SPECT, SPECT + CT, and SPECT/CT fusion imaging, respectively, and 29.7% (11/37), 27.8% (5/18), and 20.0% (1/5) of lesions were confirmed to be malignant by radiologic follow-up over at least 1 year.
Conclusions SPECT/spiral CT is particularly valuable for the diagnosis of bone metastasis in patients with known cancer by providing precise anatomic localization and detailed morphologic characteristics.

Keywords Bone lesion · Single photon emission computed tomography (SPECT) · Computed tomography (CT) · Fusion imaging

Introduction

Bone scintigraphy (BS) and computed tomography (CT) are commonly utilized means to detect bone metastases and are essential for the accurate staging and initiation of appropriate treatment [1, 2]. BS has merit for whole-body detection and has extremely high sensitivity for detecting bone metastases in some primary cancers, because even slight (5–15%) changes in local bone turnover can be detected [3]. However, the specificity of BS is low [4], because it does not provide information about the nature and composition of the lesion. Single photon emission computed tomography (SPECT) can

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overcome some of the problems associated with overlapping structures and poor anatomic localization on planar images [5], but this is often insufficient in affording a reliable and confident diagnosis [6]. In contrast, CT has the advantages of fine anatomical resolution and high specificity, but its disadvantages include relatively low sensitivity and a limited area of examination. Furthermore, the diagnostic process involving conventional multiple devices is time consuming, which can increase the patient's anxiety and delay diagnosis and therapy. An integrated SPECT/CT system combines the functional specificity of SPECT with the anatomical precision of CT as a possible solution to this dilemma [7].

Recently, a few reports assessed the value of SPECT/low-dose CT in the diagnosis of osseous metastases [8, 9], but this technique yields low-resolution anatomic images that might be insufficient for image interpretation [10]. SPECT/spiral CT can yield diagnostically sufficient CT images to provide clinicians with thorough and accurate diagnostic information, but few studies have evaluated the value of SPECT/spiral CT. Thus, the aim of our study was to investigate SPECT/spiral CT fusion imaging in the diagnosis of bone metastasis in patients with known cancer and to compare the results with SPECT alone and with SPECT + CT.

Materials and methods

Patients

From January 2007 to August 2007, 456 consecutive patients with histologically confirmed primary tumors underwent BS. One hundred and forty two (31%) patients showed at least one indeterminate lesion. In 131 patients, a SPECT/CT scan was acquired; the remaining 11 subjects underwent SPECT alone for logistic reasons. Six of the 131 patients withdrew. Finally, 141 bone lesions in 125 patients (58 women and 67 men; mean age 58.46±12.73 years; range 30–84 years) were investigated in the study. The predominant cancers were of the lung and breast (Table 1). Institutional Review Board approval was obtained, and each patient signed an informed written consent form.

System design

The hybrid SPECT/CT system incorporates a SPECT scanner and a six-detector-row CT scanner (Precedence; Philips Medical Systems, Cleveland, OH, USA).The CT bed was modified so that routine CT and SPECT scanning could be performed without moving the patient, thus reducing misregistration artifacts, because no change in the patients' positioning would be required between scans.

Table 1 Types, incidences, and percentages of primary tumors among the 125 patients

Type	Number	Percent
Lung cancer	48	38.4
Breast cancer	30	24.0
Prostate cancer	10	8.0
Gastrointestinal carcinoma	10	8.0
Esophageal carcinoma	7	5.6
Hepatocellular carcinoma	4	3.2
Endometrial cancer	3	2.4
Uterine cervix cancer	3	2.4
Lymphoma	3	2.4
Head and neck cancer	3	2.4
Renal cancer	2	1.6
Malignant melanoma	2	1.6

Bone scintigraphy

Whole-body planar imaging in the anterior and posterior positions was performed 3 h after intravenous injection of 740 MBq (20 mCi) of technetium-99m methylene diphosphonate (Tc-99m MDP). Scintigraphy was obtained with a dual-head large-field-of-view gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator.

SPECT/CT scan

On the basis of findings from planar BS, which showed indeterminate foci, the patients underwent SPECT/CT scanning. The CT scan was performed first, then the bed was positioned so that the SPECT scan could be performed immediately after the CT acquisition. The interval between SPECT and CT was less than 3 min. Both SPECT and CT were performed during tidal breathing, with the patient lying in a stable supine position. The following spiral CT acquisition parameters were used: 120 kV, 140 mA, 1.225 pitch, 512 pixel×512 pixel matrix, 6.0 mm×1.5 mm collimation, 5 mm scan, 3 mm reconstruction. The SPECT protocol was the following: 128 pixel×128 pixel matrix, 1.0 magnification factor, 360° acquisition, 180° opposed configuration, 6° steps, 30 s per frame.

Image reconstruction and fusion

SPECT data were reconstructed according to an ordered subset expectation maximization (OSEM) algorithm with four iterations and eight subsets. Images were smoothed by three-dimensional post-filtering. CT images were reconstructed with a high-resolution reconstruction algorithm (B80 kernel). SPECT and CT data were fused by Philips

Syntegra software. A workstation displayed SPECT, CT, and fused images with different percentages of SPECT and CT blending.

Image interpretation

All images were interpreted independently by two experienced nuclear medicine physicians who were aware of the primary tumor but unaware of the results of other investigations, such as symptoms and abnormal laboratory results. In cases of discrepancy, consensus was obtained by a joint reading. The degree of agreement between the two reviewers was measured with the kappa statistic. Kappa values were 0.53 for SPECT images, 0.616 for SPECT + CT images, and 0.728 for fused images.

The reporters had undergone formal CT training that included earning 100 h of CT continuing medical education credit and interpreting 500 CT cases under the supervision of a board-certified diagnostic radiologist [11]. First, the reviewers read the SPECT images. Second, 4 weeks later, the observers interpreted the SPECT + CT images. Third, a further 4 weeks later, the readers interpreted SPECT/CT images. These images were presented in random order to each of the readers at each session. Diagnosis for each lesion was visually scored with a 3-point scale: 1, definitely benign; 2, equivocal; 3, definitely malignant.

The final diagnosis was based on biopsy proof and radiologic follow-up over at least 1 year, including BS, CT, and magnetic resonance imaging. An increase in tumor size and/or a change in tumor nature (i.e., lytic or sclerotic) was considered to be malignant, whereas no change in size and/or nature over at least 1 year were regarded as benign [12].

Statistical analysis

Sensitivity, specificity, and accuracy of SPECT, SPECT + CT, and SPECT/CT fusion imaging were computed by SPSS 13.0 software (SPSS Inc, Chicago, IL, USA). Data were compared with the χ^2 test. Values of $P<0.05$ were considered to be statistically significant.

Table 2 Values (in percent) of SPECT, SPECT + CT, and SPECT/CT fusion imaging in the diagnosis of malignant lesions

Modality	Sensitivity	Specificity	Accuracy
SPECT	82.5*	66.7*	73.8*
SPECT+CT	93.7	80.8*	86.5*
SPECT/CT	98.4	93.6	95.7

*$P<0.05$, vs SPECT/CT

Table 3 Diagnostic gain (in percent) of SPECT + CT and SPECT/CT fusion imaging in 37 equivocal lesions of SPECT. Equivocal lesions were considered as incorrect lesions ($\chi^2=9.855$, $P=0.002$)

Modality	Correct	Equivocal	Incorrect
SPECT + CT	45.9(17/37)	48.7(18/37)	5.4(2/37)
SPECT/CT	81.1(30/37)	13.5(5/37)	5.4(2/37)

Results

A total of 141 areas of abnormal radiotracer uptake were depicted in 125 patients on planar scintigraphic images; 111 patients had a single lesion, 12 had two lesions, and two had three lesions. After validation, 63 lesions proved to be malignant (i.e., ten osteoblastic, 21 osteolytic, and 32 mixed lesions), and 78 proved to be benign (i.e., 50 osteophyte, 12 arthrosis, 11 fracture and five postoperative change). The diagnostic sensitivity of malignant bone disease with SPECT + CT and SPECT/CT fusion imaging was similar ($P=0.365$), but the specificity ($\chi^2=5.74$, $P=0.017$) and accuracy ($\chi^2=7.418$, $P=0.006$) of SPECT/CT fusion imaging were significantly higher (Table 2). Furthermore, the diagnostic sensitivity ($\chi^2=9.21$, $P=0.002$), specificity ($\chi^2=17.75$, $P=0$), and accuracy ($\chi^2=26.37$, $P=0$) of the SPECT/CT fusion imaging were significantly higher than those of SPECT alone (Table 2).

Among 37 equivocal lesions revealed with SPECT, the diagnostic accuracy of malignant lesions was 45.9% for SPECT + CT and 81.1% for SPECT/CT fusion imaging ($\chi^2=9.855$, $P=0.002$; Table 3). The diagnostic precision of SPECT, SPECT + CT, and SPECT/CT fusion imaging showed marked differences, depending on the anatomic region. Specifically, equivocal findings located in the spine or the ribs could be correctly classified by SPECT/CT fusion imaging (Table 4). Of the equivocal lesions revealed by SPECT, SPECT + CT, and SPECT/CT fusion imaging, the ratios of malignancy were 29.7% (11/37), 27.8% (5/18), and 20.0% (1/5), respectively (Table 5). Figures 1 and 2 provide examples of how SPECT/CT enabled the correct

Table 4 Anatomic regions exhibiting equivocal lesions on SPECT, SPECT + CT, and SPECT/CT fusion imaging

Anatomic region	SPECT	SPECT+CT	SPECT/CT
Skull	5	2	1
Axial skeleton	15	7	0
Pelvis	4	2	2
Extremities	1	1	1
Rib	12	6	1
Total	37	18	5

Table 5 Numbers and percentages of benign and malignant lesions by follow-up within equivocal lesions revealed by SPECT, SPECT + CT, and SPECT/CT fusion imaging

Modalities	Benign	Malignant	Total
SPECT	26 (70.3%)	11 (29.7%)	37
SPECT + CT	13 (72.2%)	5 (27.8%)	18
SPECT/CT	4 (80.0%)	1 (20.0%)	5

interpretation of focally increased bone uptake in different clinical situations.

Discussion

SPECT/CT fusion imaging data are beneficial for the precise detection of morphologic abnormalities from unclear scintigraphic lesions, thus resulting in a reliable diagnosis [13, 14]. The success of integrated SPECT/CT fusion imaging has heralded a new era in medical imaging in which image fusion is being increasingly accepted as reliable and accurate for ensuring precise image co-registration [15].

Our study showed that the diagnostic specificity and accuracy of malignant bone lesions were significantly higher with SPECT/CT fusion imaging than with SPECT alone or with SPECT + CT ($P<0.05$). SPECT was extremely sensitive for detecting the area of increased tracer uptake, and it could guide interpreters to determine morphologic abnormalities on corresponding CT images. Thus, SPECT/CT fusion imaging not only improved the efficiency of reading images and shortened the diagnostic process [16], but it also prevented the interpreters from missing small osteolytic or osteoblastic lesions. Side-by-side readings of unregistered or poorly registered, separately acquired image depend on the reviewer's memory and the ability of the interpreter to re-orient the images. This method is inadequate for small lesions [17].

In a study with a design that was similar to ours, Horger et al. [9] assessed the benefit of hybrid imaging for 104 lesions of 47 patients with known cancer. The diagnostic sensitivity of SPECT, SPECT + CT, and SPECT/CT fusion imaging was 94%, 100%, and 98%, respectively. Specificity was 19%, 68%, and 81%, respectively, and accuracy was 36%, 74%, and 85%, respectively. The sensitivity of SPECT/CT fusion imaging and SPECT + CT was nearly the same, but the specificity of SPECT/CT fusion imaging was significantly higher than that of SPECT + CT ($P=0.015$). The diagnostic specificity and accuracy of SPECT, SPECT + CT, and SPECT/CT fusion imaging in our study were higher than those reported by Horger et al. [9], for which there may be several possible reasons. First, a low-dose CT scanner was used by Horger et al. [9], and the lower resolution anatomic images (approximately 4 mm) [10] limited detail. Although we had a six-detector-row CT system, it may have yielded CT images of higher spatial resolution (approximately 0.7 mm), which should have depicted small anatomic structures and produced high diagnostic accuracy. Second, the acquisition time of a low performance CT system is slow (approximately 10 min), which might have increased the chances of patient movement, thus resulting in misregistration between the emission and transmission data and reducing the overall accuracy of the fusion process [18]. The acquisition time of a spiral CT scanner is faster (<1 min), thus reducing misregistration artifacts from patient positioning and changes in gastrointestinal or urinary tract contents [19]. Third, Horger et al. [9] reported that the prevalence of breast and lung cancer was 48.9% in 47 patients, and the

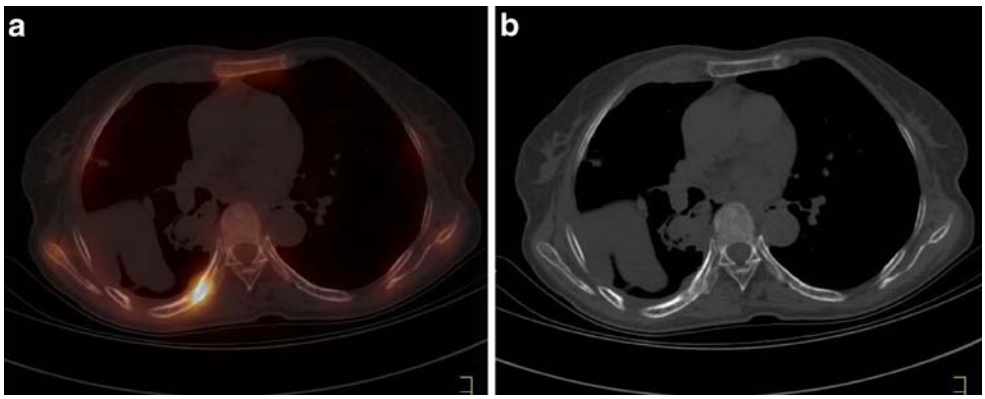

Fig. 1 Images of a 66-year-old woman with lung cancer. **a** SPECT/CT fusion image showing the increased area of activity in the posterior part of the right seventh rib. **b** CT image showing destruction of the posterior part of the right seventh rib. The final diagnosis was bone metastasis. SPECT/CT sensitive for displaying increased tracer uptake could guide interpreters to determine morphologic abnormalities on corresponding CT images. Thus, SPECT/CT fusion imaging accelerated workflow and helped the interpreters to avoid missing small lesions

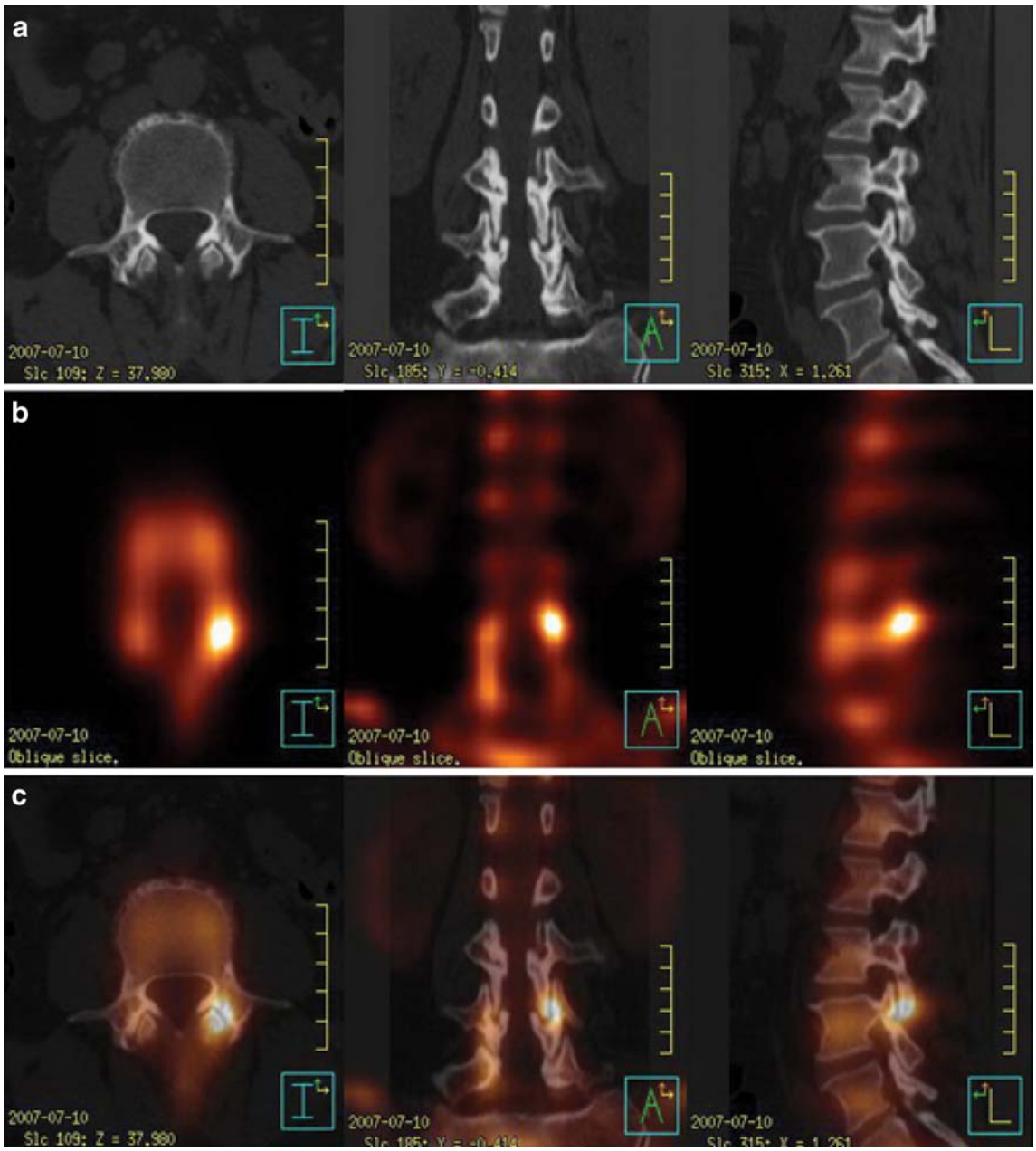

Fig. 2 Images of a 64-year-old woman with breast cancer. **a** CT image showing changes of hyperostosis and osteosclerosis in the L3 facet joint. **b** SPECT image showing that the activity is in the region of the facet joint. **c** SPECT/CT fusion image showing that the increased area of activity in the left part of L3 seen on the SPECT image matches the site of hyperostosis and osteosclerosis in the facet joint seen on the CT image. The final diagnosis was of degenerative change

prevalence of head and neck cancer was 17.0%. In our series the former was 62.4% in 125 cases and the latter was 2.1%. Therefore, the different percentages of primary tumors may have affected diagnostic specificity and accuracy.

In our group, for 37 equivocal lesions on SPECT, the diagnostic accuracy of SPECT/CT fusion imaging was significantly higher than that of SPECT + CT (P=0.002), which may have been the result of the following. First, SPECT + CT might not have provided precise localization to allow for conditions such as costovertebral arthritis and vertebral osteomyelitis. Second, osteolysis was located medially only a few millimeters from the facet joint in the lamina, and the interpreters reviewing the SPECT + CT images may have tended to misdiagnose the increased bone metabolism as a degeneration of the facet [16, 20]. Third, especially difficult was the differentiation of the bone island from slightly sclerotic change (early sclerotic metastasis) on

SPECT + CT images. Fourth, metastatic foci representing slight changes may have been overlooked on SPECT + CT images which could be detected on fused images.

In our study, for equivocal findings from SPECT, SPECT + CT, and SPECT/CT fusion imaging, the ratio of malignancy was 29.7% (11/37), 27.8% (5/18), and 20.0% (1/5), respectively, by follow-up. Clarification of the nature of the indeterminate lesions was important, because the differentiation between malignant and benign lesions is very helpful for guiding patient care. Early diagnosis of bone metastases could influence additional or intensified treatment [21], which in turn may prolong survival and improve quality of life. Early diagnosis of benign bone lesions would exclude the need for chemotherapy or radiotherapy, which would lessen the economic burden and stress for patients. SPECT/CT enables a one-stop approach to bone lesion characterization while shortening the diagnostic process, improving patient care and reducing patient anxiety.

Several limitations in our study should be noted. First, a detailed bone histopathologic analysis (five patients) was not feasible. We confirmed bone metastasis on the basis of radiologic follow-up (120 patients). A small proportion of bone metastases, such as in breast cancer, could remain unchanged in appearance despite lack of therapy. Change in a lesion (such as infection and aneurysmal bone cyst) within 1 year does not prove that a lesion had been a metastasis. Second, the patients at our hospital might not be considered typical of other centers, and the findings might be considered to be relatively institution-specific. Third, we analyzed our data only on a lesion-by-lesion basis and not on a per patient basis.

Multicenter, prospective studies will be needed to show the specific clinical indications for, and the cost effectiveness of, SPECT/CT fusion imaging. Further studies should also compare the value of SPECT/CT with other modalities, such as [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography/CT or whole-body magnetic resonance imaging, in detecting osseous metastases [22–24].

Conclusions

SPECT/CT fusion imaging outperformed side-by-side reading of SPECT + CT data. It is particularly valuable in the diagnosis of bone metastasis in patients with known cancer because of precise anatomic localization and detailed CT morphologic characteristics of radiotracer uptake.

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